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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/712,338	11/13/2000	Alexander Blinkovsky	4990.210-US	8547
25907	7590	12/16/2003	EXAMINER	
NOVOZYMES BIOTECH, INC.			SWOPE, SHERIDAN	
1445 DREW AVE				
DAVIS, CA 95616			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/712,338

Applicant(s)

BLINKOVSKY ET AL.

Examiner

Sheridan L. Swope

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 August 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 30-49 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 30,31,36 and 38-49 is/are rejected.
- 7) ☒ Claim(s) 32-35 and 37 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 13 November 2000 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 1100.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

Applicant's election with traverse of species (g), N-CBZ-Ala-Phe, in the response received August 27, 2003 is acknowledged. The basis of the traversal is that there would not be a serious burden on the examiner if election were not required because the polypeptide having carboxypeptidase activity has the ability to hydrolyze X from N-CBZ-Ala-X wherein X is any amino acid. This is not found to be persuasive. Applicants have not provided evidence that all carboxypeptidases are able to cleave X from N-CBZ-Ala-X, wherein X is any amino acid. Furthermore, a search for a polynucleotide encoding a polypeptide able to hydrolyze N-CBZ-Ala-X, wherein X is a Phe, may not encompass a search for a polynucleotide encoding a polypeptide able to hydrolyze N-CBZ-Ala-X, wherein X is Ile, Glu, Lys, Arg, Asp, Asn, or Tyr and searching for all said polynucleotides would present a burden on the Office. The requirement is still deemed proper and is therefore made FINAL.

Applicant's cancellation of Claims 1-29 and amendment of Claim 47 is acknowledged. Claims 30-49 are pending and are hereby considered on their Merits.

Specification-Objections

The specification is objected to because figure 4 is not labeled "Fig 4". Correction is required.

The specification is objected to for misspelling, throughout the specification, the name "Svendsen".

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 recites "The nucleic acid sequence of claim 34, which encodes a polypeptide consisting of amino acids 19-555 of SEQ ID NO: 2, while Claim 34 recites "The nucleic acid sequence ..., which encodes a polypeptide consisting of the amino acid sequence of SEQ ID NO: 2". The nucleic acid sequence of Claim 35 cannot consist of a molecule wherein residues 1-18 are simultaneously present and not present. It is suggested that applicants amend Claim 35 to depend from Claim 33, which includes fragments of SEQ ID NO: 2.

Claim 39 is indefinite for reciting "high stringency" on line 2 and "wherein medium stringency conditions are..." on line 4. Correction is required. For purposes of examination, it is assumed that "wherein medium stringency conditions are..." on line 4 is meant to be "wherein high stringency conditions are...".

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 31, 36, 38, 40, 42-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated nucleic acid molecules encoding SEQ ID NO: 2 or fragments thereof having carboxypeptidase activity, does not reasonably provide enablement for any nucleic acid molecule (i) encoding any protein having at least 70% identity with residues 19-555 of SEQ ID NO: 2, (ii) having at least 70% identity with SEQ ID

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NO: 1 or residues 55-1662 of SEQ ID NO: 1, (iii) which hybridizes under medium stringency with residues 55-1662 of SEQ ID NO: 1, or at least 100 nucleotides thereof, or the complement thereof, (iv) encoding a polypeptide having carboxypeptidase activity with optimal activity in the pH range of 4-5, in the temperature range of 55°-60°C, with residual activity of 65% after 30 minutes, and the ability to hydrolyze Phe from N-CBZ-Ala-Phe, or (v) encoding the polypeptide of (iv), wherein the polynucleotide is from a strain of *Aspergillus*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 30 is so broad as to encompass any polynucleotide sequence (i) encoding any protein having at least 70% identity with residues 19-555 of SEQ ID NO: 2, (ii) having at least 70% identity with residues 55-1662 of SEQ ID NO: 1, (iii) which hybridizes under medium stringency with at least 100 nucleotides of SEQ ID NO: 1 or the complement thereof, (iv) any active fragment of (i)-(iii), or (v) encoding a polypeptide having carboxypeptidase activity with optimal activity in the pH range of 4-5, in the temperature range of 55°-60°C, with residual activity of 65% after 30 minutes, and the ability to hydrolyze Phe from N-CBZ-Ala-Phe (as per the species election). Claim 31 is so broad as to encompass any polynucleotide sequence encoding any protein having at least 70% identity with residues 19-555 of SEQ ID NO: 2. Claim 36 is so broad as to encompass any polynucleotide sequence having at least 70% identity with SEQ ID NO: 1. Claim 38 is so broad as to encompass any polynucleotide sequence which hybridizes under medium stringency with nucleotides 55-1662 of SEQ ID NO: 1, to a subsequence thereof having at least 100 nucleotides of SEQ ID NO: 1, or a complementary strand thereof. Claims 40, 46, and 47 are so broad as to encompass any polynucleotide encoding

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a polypeptide having carboxypeptidase activity with an optimal activity in the pH range of 4-5 at 25°C, an optimal activity in the temperature range of 55°-60°C at pH 4, with a residual activity of 65.5% after 30 minutes at pH 4 and 60°C, and the ability to hydrolyze Phe from N-CBZ-Ala-Phe. Claim 48 is so broad as to encompass any polynucleotide sequence of Claim 46 obtained from *Aspergillus* or a telemorph thereof. Claim 49 is so broad as to encompass any polynucleotide sequence of Claim 46 obtained from *Aspergillus oryzae* or a telemorph thereof. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired carboxypeptidase activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to the amino acid sequence of SEQ ID NO 2 and the nucleotide sequence of SEQ ID NO 1.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art

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would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the Claims 30, 31, 36, 38, 40, and 46-49, which encompass any nucleic acid molecule (i) encoding any protein having at least 70% identity with residues 19-555 of SEQ ID NO: 2, (ii) having at least 70% identity with SEQ ID NO: 1 or residues 55-1662 of SEQ ID NO: 1, (iii) which hybridizes under medium stringency with residues 55-1662 of SEQ ID NO: 1, or at least 100 nucleotides, or the complement thereof, (iv) encoding a polypeptide having carboxypeptidase activity with optimal activity in the pH range of 4-5, in the temperature range of 55°-60°C, with residual activity of 65% after 30 minutes, and the ability to hydrolyze Phe from N-CBZ-Ala-Phe, or (v) encoding a polypeptide having carboxypeptidase activity with optimal activity in the pH range of 4-5, in the temperature range of 55°-60°C, with residual activity of 65% after 30 minutes, and the ability to hydrolyze Phe from N-CBZ-Ala-Phe, wherein the polynucleotide is from a strain of *Aspergillus*. The specification does not support the broad scope of Claims 30, 31, 36, 38, 40, and 46-49 because the specification does not establish: (A) regions of the protein structure which may be modified without effecting the activity of the recited carboxypeptidase activity; (B) the general tolerance of the activity of the recited carboxypeptidase activity to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices of modification of the polynucleotide of SEQ ID NO: 1, or encoding SEQ ID NO: 2, is likely to be successful.

Since Claims 42-45 further recite vectors, host cells and methods of expressing the nucleic acids of Claim 30, Claims 42-45 are also rejected under 35 U.S.C. 112 first paragraph due to lack of enablement for the same reasons discussed above.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number polynucleotides encoding carboxypeptidases with an enormous number of amino acid modifications of the carboxypeptidase of SEQ ID NO: 2. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim 41 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The invention employs novel cells (NRRL B-21616). Since the cells are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the cells. It is noted that applicants have deposited the organisms (page 47) but there is no indication in the specification as to public availability. Since the deposit was made under the terms of the Budapest Treaty, an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration

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number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

Claims 30, 31, 36, 38, and 40, 42-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of nucleic acid molecules comprising (i) polynucleotides that hybridize under medium stringency with residues 55-1662 of SEQ ID NO: 1, or at least 100 nucleotides, or the complement thereof or (ii) polynucleotides encoding polypeptides having carboxypeptidase activity with optimal activity in the pH range of 4-5, in the temperature range of 55°-60°C, with residual activity of 65% after 30 minutes, and the ability to hydrolyze Phe from N-CBZ-Ala-Phe. The specification teaches the structure of only a single representative species of such polynucleotides, SEQ ID NO: 1. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the ability to hybridize under medium stringency with residues 55-1662 of SEQ ID NO: 1, or at least 100 nucleotides or the complement thereof, and encoding a carboxypeptidase, or encoding polypeptides having carboxypeptidase activity with optimal activity in the pH range of 4-5, in the temperature range of 55°-60°C, with residual activity of 65% after 30 minutes, and the ability to hydrolyze Phe from N-CBZ-Ala-Phe. The genus of nucleic acid molecules having the recited structural feature of the genus (i.e., the ability to hybridize under medium stringency with residues 55-1662 of SEQ ID NO: 1, or at least 100 nucleotides or the complement thereof) is a

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large and variable genus and those species encoding a carboxypeptidase do not constitute a substantial portion of said genus of nucleic acid molecules. Furthermore the structure of the genus of polynucleotides encoding polypeptides with carboxypeptidase activity and having optimal activity in the pH range of 4-5, in the temperature range of 55°-60°C, with residual activity of 65% after 30 minutes, and the ability to hydrolyze Phe from N-CBZ-Ala-Phe is completely undefined. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 30, 40, 46, and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Svendsen et al, 1993, as evidenced by Hoffman et al, 1976, in view of Metzler et al, 1977. Svendsen et al, teach the amino acid sequence of a carboxypeptidase previously characterized by Hoffman et al. As shown by Hoffman et al, said carboxypeptidase has optimal activity at pH 4.3 (p597, parg 4) and is stable at pH 4 for prolonged times (p593, parg1). The carboxypeptidase of Hoffman et al can hydrolyze N-CBZ-Ala-Ala (Table III), as well as cleaving terminal isoleucine, glutamic acid, lysine, arginine, aspartic acid, asparagine, phenylalanine, and tyrosine residues from peptides (Table IV). Although Svendsen et al teach the amino acid sequence of the

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carboxypeptidase, they do not teach the polynucleotide sequence encoding the carboxypeptidase. However, the polynucleotide sequences encoding any known polypeptide sequence can be deduced from the genetic code, as taught by Metzler et al. It would have been obvious to a person of ordinary skill in the art to use the genetic code to deduce all the nucleic acid sequences that can encode the polypeptide of Svendsen et al. Motivation to do so derives from the advantage of using said deduced sequences to produce the carboxypeptidase of Svendsen et al. The advantages of recombinant production of proteins are well known in the art. Therefore, Claims 30, 40, 46, and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Svendsen et al, 1993, as evidenced by Hoffman et al, 1976, in view of Metzler et al, 1977.

Allowable Subject Matter

Claims 32-35 and 37 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 703-305-1696. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

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Rubena Lundy
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